American Journal of Hematology 53:234–238 (1996)

# On the Value of Menorrhagia as a Predictor for Coagulation Disorders

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**The value of menorrhagia as a predictor for mild bleeding disorders has been very little studied and the results are divergent. In the present study on 30 women with objectively verified menorrhagia, we found a significantly increased prevalence of von Willebrand's disease (20%). By keeping a strict sampling and laboratory routine, and by restricting sampling to cycle days 5–7, we also obtained a very low interindividual variation of von Willebrand factor and coagulation factor VIII. We conclude that menorrhagia is a valuable predictor for coagulation and platelet disorders, and that time of sampling is of importance. This should be considered in the investigation of menorrhagia, and can be a guideline in looking for mild bleeding disorders.** © 1996 Wiley-Liss, Inc.

**Key words: menorrhagia, von Willebrand's disease, coagulation disorder, platelet dysfunction, predictor**

## INTRODUCTION

The value of menorrhagia as a predictor for mild bleeding disorders has been very little studied, and the results are divergent [1,2]. One reason for this may be that in clinical practice, the correlation between anamnestic and true menorrhagia (blood loss exceeding 80 ml per cycle) is poor. In women reporting excessive menstrual blood loss, only some 50% will be found to have objectively verifiable menorrhagia [3–6]. The value of menorrhagia as a predictor is also influenced by the fact that women with heavy menstruation seldom consult a physician to obtain help [2,7]. Despite this, the clinical benefit of finding a coagulation disorder in women with menorrhagia is obvious, and previous papers on the subject have recommended consideration of a coagulation disorder in the assessment of women with menorrhagia [8].

In the present paper, we want to point out that the chances of finding a coagulation disorder when examining a woman with menorrhagia are considerable, a fact that might well guide us in our choice of therapy. We chose in particular to analyze P-coagulation factor VIII (F VIII), P-von Willebrand factor (vWF), and Pt-capillary bleeding time (BT), since mild von Willebrand's disease (vWD) and platelet dysfunction are the most common bleeding disorders.



## MATERIALS AND METHODS

### Subjects With Menorrhagia

Thirty Caucasian women (age 24–48 years, mean age 39 years) with a history of regular and large menstruation (inclusion criterion, >80 ml blood loss/cycle) were examined while participating in a clinical study of treatment of menorrhagia, as previously reported [9]. During two run-in cycles without any treatment, blood loss was objectively quantified by determination of the lost amount of hemoglobin. The women were instructed to collect their menstrual blood; it was emphasized that waste of blood must be avoided. Blood in towels and tampons was extracted with a 5% NaOH solution, thus transforming the hemoglobin into alkaline hematin, which was estimated spectrophotometrically at 540 nm. The lost amount of blood in milliliters was calculated from the loss of hemoglobin and the hemoglobin concentration in venous blood [10].

None of the participating women had taken any medi-

Received for publication September 4, 1995; accepted July 10, 1996.

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cation containing sex hormones during the 2 months preceding the investigation. Preparations for the tests also included abstinence from acetylsalicylic acid and nonsteroidal antiinflammatory drugs for the 10 days preceding blood sampling. During the study, blood loss was measured for five consecutive cycles with 0–2 months' interruption in connection with vacation, etc.

### Blood Sampling

At the beginning and end of the clinical study, standard blood samples were analyzed according to hospital routines.

For analysis of hemostatic values, blood was collected from cycle days 5–7, where the first day of bleeding was taken as day 1, during the two untreated cycles. Samples were collected between 8–12 AM, the patients having abstained from fat-containing food during the morning before sampling, and in connection with the first sampling a bleeding history was established. Each sampling was also completed with a Pt-capillary bleeding-time (BT) measurement using a Simplate II device [11] (General Diagnostics, Organon Teknika, Turnhout, Belgium). Samples for hemostatic variables were obtained by direct venipuncture, using light stasis applied only for venipuncture. Blood was allowed to run directly into siliconized vacuum tubes (Becton Dickinson, Plymouth, UK) containing buffered (pH 7.4) trisodium citrate (0.129 mol/l, 1 part + 9 parts blood) and thoroughly mixed. Samples were centrifuged for 20 min at 3,000*g*, and the plasma was aliquoted in polypropylene tubes, one for each assay, and frozen at −70°C until analyzed.

### Laboratory Methods

**General assays.** B-hemoglobin, B-hematocrit, S-ferritin, B-platelets, S-creatinine, P-alkaline phosphatase, P-bilirubin, S-alanine-aminotransferase, S-aspartate-aminotransferase, and differential counts were analyzed using fresh samples, according to routine.

**Coagulation assays.** Amidolytic methods with synthetic chromogenic peptide substrates were applied for measurements of F VIII with the S-2765 substrate [12], P-coagulation factor X (F X) with the S-2222 substrate [13], and P-plasmin inhibitor (earlier named $\alpha_2$-antiplasmin) with the S-2251 substrate [14]. Analyses were done on a Cobas Bio (Roche, Basel, Switzerland) autoanalyzer.

Enzyme-linked immunosorbent assays (ELISA) were used for analysis of vWF antigen (vWF:ag) [15] using reagents from IMCO (Stockholm, Sweden), and for analysis of D-dimers [16] using reagents from MabCo (Springwood, Australia). Absorbance was measured with the spectrophotometer (Dynatech MR 7000 (Dynatech Laboratories, Ltd., Billingshurst, UK). An ACL ultracentrifugal analyzer (Il, Paderno Dugnano, Italy) was used for measuring activated partial thromboplastin time (APTT) (now named plasma-coagulation, surface-induced time) using Cephotest reagent from Nycomed (Oslo, Norway), and for measuring the international normalized ratio (corresponding to prothrombin time, now named plasma-coagulation, tissue factor-induced time) using Stago prothrombin complex assay reagents from Triolab (Mölndal, Sweden). P-fibrinogen was analyzed by measuring the fibrin polymerization time [17] with an Electra 900C instrument (Medical Laboratory Automation, Pleasantville, NY).

**TABLE I. Interindividual Correlation Between Samples Taken on Occasions A and B***

| | vWF A, cycle 1 | vWF B, cycle 2 |
|---|---|---|
| vWF A | 1.000 | 0.948 |
| vWF B | 0.948 | 1.000 |
| | F VIII A, cycle 1 | F VIII B, cycle 2 |
| F VIII A | 1.000 | 0.861 |
| F VIII B | 0.861 | 1.000 |

*$P < 0.0001$.

For F VIII and vWF:ag, the range 0.5–1.5 IU/ml is considered normal; the ranges in most of our control materials were skewed and wider [1,18]. Normal range for the F VIII/vWF:ag ratio was set to 0.6–1.6, according to earlier control materials [19]. The upper limit for normal Pt-capillary bleeding time is suggested by the manufacturer to be 9.5 min (570 sec). This value correlates well with values we found in two series of healthy controls; it is also used by the central laboratory at our hospital.

### Statistics

Descriptive statistics and correlation tables were calculated using Statview 4.0® (Abacus Concepts, Berkeley, CA) run on a Macintoch LC 475. In comparing the prevalence of vWD in the population and in our group, the chi-square test was used.

## RESULTS

Menstrual blood loss during the two untreated cycles was, on average, 246 ml, ranging from 82–554 ml.

Interindividual variation regarding F VIII and vWF was very low, with a correlation between the two sampling occasions of 0.948 for vWF and 0.861 for F VIII (Table I).

Of the 30 women investigated, 6 were found to probably suffer from mild von Willebrand's disease (vWD), since their vWF:ag levels were low or on the verge of the lower normal level, and since many other criteria for hemorrhagic diathesis were fulfilled (Table II). Three out of these 6 women had, in addition to low vWF:ag levels, a pathologically elevated F VIII/vWF:ag ratio of >2 on all sampling occasions, and 2 women had a prolonged bleeding time, which strengthens the diagnosis of vWD, most probably type I [19–21]. Six patients with vWD out

**TABLE II. Data on Six Women Characterized as Having vWD***

| Patient no. | vWF | F VIII | F VIII/vWF | Bleeding time (sec) | Bleeding propensity | MBL (ml) |
|---|---|---|---|---|---|---|
| 16 | 0.54 | 0.74 | 1.37 | 555 | +++ | 271 |
| 21 | 0.53 | 1.29 | 2.43 | 315 | + | 87 |
| 24 | 0.49 | 0.52 | 1.06 | 768 | + | 250 |
| 26 | 0.55 | 1.17 | 2.13 | 565 | ++ | 158 |
| 27 | 0.55 | 0.66 | 1.2 | 420 | +++ | 256 |
| 30 | 0.50 | 1.16 | 2.32 | 510 | ++ | 153 |

*Coagulation factor levels, bleeding time values, and menstrual blood loss are the mean of the two values obtained on sampling occasions A and B (untreated cycles). Grading of bleeding propensity: 0, none; +, one of following symptoms: frequent nose-bleeding, easy bruising, menorrhagia, abnormal bleeding after tooth extraction, or close relative with bleeding tendency; ++, two symptoms; +++, three or more symptoms. MBL, menstrual blood loss.

**TABLE III. Data From Six Women With vWD and 24 Women Without vWD, on Sampling Occasions A and B***

| | WD, mean (SD) | Not vvWD, mean (SD) | *P* |
|---|---|---|---|
| vWF | | | |
| First cycle (A) | 0.54 (0.02) | 1.18 (0.46) | 0.002 |
| Second cycle (B) | 0.52 (0.04) | 1.16 (0.47) | 0.003 |
| FVIII | | | |
| First cycle (A) | 0.96 (0.36) | 1.23 (0.48) | 0.209 |
| Second cycle (B) | 0.89 (0.31) | 1.24 (0.58) | 0.211 |
| FVIII/vWF | | | |
| First cycle (A) | 1.80 (0.68) | 1.12 (0.49) | 0.009 |
| Second cycle (B) | 1.64 (0.52) | 1.12 (0.68) | 0.089 |
| BT | | | |
| First cycle (A) | 563 (177) | 462 (143) | 0.150 |
| Second cycle (B) | 481 (149) | 463 (118) | 0.754 |

*Untreated cycles.

of 30 examined makes 20%, which is significantly more ($P = 0.001$) than the expected 2%.

In the other 24 patients, one had a low value of F X, i.e., 0.68 IU/ml. This patient otherwise had normal laboratory values, including APTT and bleeding time. High values of D-dimers without known cause were found in 2 of the 24 patients. Apart from this, all patients fell within the coagulation parameters described in Laboratory Methods, and within the normal range stated by our laboratory, with no clinically significant deviations in the general assays.

Table III shows coagulation data for the present group of 6 along with the 24 women we considered healthy apart from menorrhagia.

Eight of the 30 women had at one or both sampling occasions a prolonged BT. Of these women, 5 were not in the group with suspected vWD. Most probably suffer from a platelet dysfunction.

All patients were also asked about observed tendency toward increased bleeding or about relatives with bleeding disorders, as is the routine in our coagulation investigations (Table II).

## DISCUSSION

The prevalence of mild vWD in the population was estimated at 0.8–1.3% in two earlier studies [22,23]. The prevalence in Scandinavia, however, has been estimated to be higher [20]. In findings using 20 female blood-donors without known bleeding disorders, age 20–40 years, sampled in 1986 in our laboratory, we found a mean vWF:ag ELISA of 0.98 IU/ml, with a range from 0.54–1.98 IU/ml and SD of 0.36. These women were not sampled on cycle days 5–7, and therefore these values might be lower in other parts of the cycle. Unpublished data from an earlier study [24] are presented in Table IV. The level of vWF in plasma is influenced by many factors such as age, blood group, hormones, and smoking, and therefore the diagnosis of the mild form of vWD can be as complex as shown by Zhang et al. [21]. In the absence of a genetic analysis, the diagnosis must be established by the presence or absence of several other factors, especially as even patients with known vWD-mutations sometimes have a vWF:ag level well above the lower limit [19,21]. Even if we calculate as high a prevalence as 2%

**TABLE IV. Data From 12 Healthy Women Without Increased Propensity to Bleed, Sampled on Cycle Days 5 or 6***

| | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|
| vWF | 0.90 | 0.23 | 0.59 | 1.44 |
| FVIII | 1.00 | 0.20 | 0.77 | 1.45 |
| FVIII/vWF | 1.15 | 0.27 | 0.86 | 1.75 |

*Further described in Blombäck et al. [24].

in the population, we have with our 20% a significantly ($P < 0.001$) increased frequency of vWD in our material on healthy women without other known bleeding disorders other than menorrhagia.

Severe forms of bleeding disorders are most often easily suspected and diagnosed. The milder forms, on the other hand, can go undiagnosed, although they can be of great medical importance. In addition, knowledge of patients with vWF:ag levels at about 0.5 can be of significance, even if they lack the genetic defect. It seems as though women with excessive menstrual blood loss are overrepresented in this group. This implies a high predictive value for anamnestic menorrhagia when we are looking for bleeding disorders. The increased frequency of prolonged bleeding time in patients without vWD may also indicate that the reason for menorrhagia in some cases is platelet dysfunction. Moreover, more rare deficiencies of other coagulation factors could be the cause of increased bleeding in these patients.

A great intraindividual variation in vWF:ag and F VIII, especially in patients with vWD, was described by Abildgaard et al. [25], and may in part be related to the menstrual cycle, as suggested by Mandalaki et al. [26]. The most representative values of vWF:ag and F VIII, when looking for bleeding disorders, are found early in the menstrual cycle, probably not later than day 7 in the cycle, as shown by Blombäck et al. [20,24]. In the present study, we obtained a very low interindividual variation by restricting sampling to cycle days 5–7, and by keeping a strict sampling and laboratory routine.

## CONCLUSIONS

Our study shows that the prevalence of coagulation disorders may be substantially higher in women with menorrhagia. The time of sampling is of significant importance. These facts are to be considered in the examination of women with excessive menstrual blood loss, in order not only to achieve the best possible results of treatment, but also to unveil undiagnosed coagulation disorders. This will prove of importance, for instance, in the event of acute surgery and reproductive events such as delivery and abortion. In these women, it also seems wise to avoid planned surgery during the first 7 days of the menstrual cycle. As this study was performed on a small number of patients and involved the difficult diagnosis of vWD, we feel that further studies are needed.

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